5.2 Key limitations of current framework of case incident reporting	2
5.3 Proposal for improvement of current framework of case incident reporting	2
6.1 The risk assessment process	6
6.2 Assessment of the reliability of individual epidemiological studies	4
6.3 Assessment of strength of evidence of epidemiological studies	2
6.3.2 Meta-analysis as a tool to explore heterogeneity across studies	2
6.3.3 Usefulness of meta-analysis for hazard identification	6
6.3.4 Pooling data from similar epidemiological studies for potential dose-response modelling	2
7. Integrating the diverse streams of evidence: human (epidemiology and vigilance data) and experimental information	4
7.1 Sources and nature of the different streams of evidence. Comparison of experimental and epidemiological approaches	5
7.2 Principles of weighting observational and laboratory animal experimental data	6
7.3 Weighting all the different sources of evidence	3
7.4 Biological mechanisms underlying the outcomes	6
7.5 Adverse outcome pathways (AOPs)	1
7.6 Novel tools for identifying biological pathways and mechanisms underlying toxicity	1
7.7 New data opportunities in epidemiology	5
8. Overall recommendations	2
8.1 Recommendations for single epidemiological studies	9
8.2 Surveillance	1
8.3 Meta-analysis of multiple epidemiological studies	1
8.4 Integration of epidemiological evidence with other sources of information	2
9. Conclusions	6
Annex A – Pesticide epidemiological studies reviewed in the EFSA External Scientific Report and other reviews	2
Annex B – Human biomonitoring project outsourced by EFSA	1
Annex C – Experience of International regulatory agencies in regards to the integration of epidemiological studies for hazard identification	1
Annex D – Effect size magnification/inflation	3

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Table 2: Comments received on the draft opinion per organisation

Organisation	Country	Number
Board for the Authorisation of Plant Protection products and Biocides	The Netherlands	10
Centre F Baclesse	France	22
City of Hope	USA	1
Health & Safety Executive	UK	7
Istituto Superiore di Sanità	Italy	13
European Crop Protection Association (ECPA)	Belgium	39
Food Chain Safety Office	Hungary	6
German Federal Institute for Risk Assessment (BfR)	Germany	10
International Society for Environmental Epidemiology	Polland	1
Institute of public Health	Belgium	6
LaKind Associates, LLC	USA	2
Ministero della Salute	Italy	15
National Institute of Occupational Health (STAMI)	Norway	2
Personal	USA	13
Retired Epidemiologist	USA	15
Syngenta	UK	16
Université de Bordeaux	France	29
University of California (UCLA)	USA	5
Uniformed Services University	USA	3
University of Cincinnati	USA	1
University of Iowa	USA	2
US EPA	USA	5

3. Conclusions

The stakeholders submitted many valuable and detailed comments and individual answers to each comment are given in the appendix to this report showing also the comments were taken up for the finalisation of the Scientific Opinion. EFSA has duly considered these comments and revised the draft scientific opinion where necessary.

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Appendix A – EFSA responses to stakeholder comments and questions

No	Organization	Country	Chapter	Comment - Part 1
1	German Federal Institute for Risk Assessment (BfR)	DEU	General comments	The BfR appreciates the informative and comprehensive scientific opinion! To our understanding, the Scientific Opinion is considered as a tool for the evaluation (and integration) of existing epidemiological studies, predominantly for a.s. renewal and/or an evaluation within the framework of a vigilance process, if applicable. However, regarding the parts addressing the conduct of single epidemiological studies (e.g. 8.1, lines 2365 ff, pp 56ff), it is not clear to whom they are directed. The conduct of epidemiological studies is not part of data requirements according to Reg. (EC) No. 1107/2009 (only evaluation of existing studies). Hence, epidemiological studies will probably not be conducted within the framework of Reg. (EC) No. 1107/2009. Do you consider the Scientific Opinion to be read as a "guidance" on how epidemiological studies must be conducted (who ever would conduct them), which information must be reported, and how they have to be evaluated in order to be integrated in the risk assessment of pesticides? *EFSA Response:* *Regulation (EU) No 1107/2009 lays down "where available, and supported with data on levels and duration of exposure, and conducted in accordance with recognised standards, epidemiological studies are of particular value and must be submitted". Hence, epidemiological studies are requested to meet recognized standards to be used for pesticide risk assessment, and section 8.1 (Recommendations for single epidemiological studies) intends to provide these standards.* *The mandate was to prepare a Scientific Opinion and not a "guidance". The following text has been added in line 2366: "The following recommendations for improving epidemiological studies are aimed to conform to the 'recognised standards' mentioned in Regulation (EU) No 1107/2009 to make them of particular value to risk assessment of pesticides ("where available, and supported with data on levels and duration of exposure, and conducted in accordance with recognised standards, epidemiological studies are of particular value and must be submitted"). Accordingly, these recommendations can indeed not be considered as a practical guidance for researchers on how to conduct such studies, but for those who are planning to conduct a study for further use in pesticide risk assessment."*

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2	ECPA	BEL	General comments	ECPA welcomes this initiative of the PPR Panel to provide a scientific opinion on the current state of epidemiology studies on pesticides, to provide recommendations for how to improve future studies and to provide guidance on how epidemiology studies could be used to strengthen the risk assessment of pesticide active substances in the EU. We concur with the Panel's conclusions on the state of current epidemiology studies and with most of the recommendations put forward on how to improve future studies. This scientific opinion also captures many important concepts that should be considered when evaluating epidemiology studies, particularly in considering their use in the context of a risk assessment. However, one point we would highlight is that, while some of the PPR Panel's recommendations are likely to work in an ideal setting, it is unlikely they will be feasible based on the studies which are currently available (e.g. it is often impossible to get data beyond ever/never use of a pesticide). It would be helpful if the scientific opinion provided further guidance on what should be done if high-quality studies are not available for a particular pesticide. For example, the opinion cites several general, minimum quality and reporting guidelines for epidemiology studies, but does not indicate whether EFSA will require adherence to these guidelines when considering epidemiology studies for the purposes of setting quantitative limits (e.g. pesticide residue limits) or for the purposes of hazard assessment. At present, toxicity studies submitted to EFSA must comply with good laboratory practice (GLP) guidelines, but unfortunately a similar set of requirements are not codified for epidemiology studies. The stated objective of the scientific opinion is to facilitate the appropriate use of epidemiology evidence in pesticide risk assessment, to achieve this goal in practice a clear list of these quality and reporting requirements would be beneficial. It would be useful to understand if such more prescriptive guidance is expected to be developed by EFSA as a follow-up to this scientific opinion. *EFSA Response:* *This document is a Scientific Opinion, and must not be seen as a guidance. The Opinion is expected to be refined in the future and the development of a guidance might be considered.* *Regulation (EU) No 1107/2009 lays down that epidemiological studies with "recognised standards" are of particular value for pesticide risk assessment and must be submitted. For these reasons, sections 6.2 and 8.1 of this Opinion list a number of quality and reporting requirements that should be fulfilled by epidemiological studies in order to be submitted for risk assessment. Also, section 6.2 indicates that low quality studies, although be included in a systematic review, they will not be further considered for risk assessment.* In addition, the opinion does not present explicit recommendations specifically for incorporating epidemiology evidence in systematic reviews – i.e. it does not specify how EFSA will consider epidemiology studies in light of animal and other evidence streams to form conclusions regarding hazard and risk (e.g., in situations where there is discordance in the lines of evidence from epidemiology studies and toxicological studies). The opinion would benefit from an additional discussion of evidence integration and an explicit discussion of EFSA's plans to follow such recommendations. *EFSA Response:* *In line 329 of the Opinion it is said "epidemiological studies should be retrieved from the literature according to the*

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				EFSA Guidance entitled Submission of scientific-peer reviewed open literature for the approval of pesticide active substances under Regulation (EC) No 1107/2009" (EFSA 2011a), which follows the principles of the Guidance "Application of systematic review methodology to food and feed safety assessments to support decision making" (EFSA 2010). *Situations where there is discordance between epidemiology and toxicological studies should be addressed on a case-by-case basis and the available evidence weighed. Lines 2136-2138 of the Opinion state "In case of non-concordance... for hazard identification, the data suggesting the presence of a hazard should generally take precedence. For dose–response the data resulting in the lower acceptable level should take precedence." For the time being it is too premature to formulate specific guidance on the different situations of non-concordance and the Opinion indicates that "efforts should be made to develop a better understanding of the biological basis for the contradiction".*
3	ECPA	BEL	General comments	The individual sections merge discussions of epidemiology study design issues and specific PPR Panel opinions and recommendations, such that the Panel's conclusions are often difficult to find. The "Overall Recommendations" section provides a list of "ideal" conditions for the conduct and use of epidemiology data, but does not explicitly indicate how these recommendations will be incorporated into EFSA risk assessments. In the "Conclusions" section, it remains somewhat unclear what is planned beyond "considering" the overall strengths and weakness of epidemiology studies and "identifying areas" for improvement in the use of epidemiology evidence in pesticide risk assessment in the EU. In order to provide sufficient guidance, it would be useful if the opinion explicitly stated what will be required (e.g. a minimum level of study quality) for epidemiology evidence in EFSA risk assessments for pesticide active substances. *EFSA Response:* *Because of the nature of this Opinion, a clear-cut conclusion cannot be provided. For this reason, conclusions are elaborated based on the Terms of Reference of the Opinion and for each point cross references to specific sections in the Opinion are provided.* *As mentioned in comment #2, the quality assessment of epidemiological studies is addressed in section 6.2 of the Opinion.* It would be useful if the PPR Panel placed greater emphasis on the difference between hypothesis testing and hypothesis-generating exploratory research and the value for regulatory decision taking. Exploratory research is (generally) conducted with the understanding that results will need to be confirmed in future research before they can be used for regulatory decision making. Studies with a specific a priori hypothesis on the other hand are more likely to contribute evidence relevant for regulatory decision making. *EFSA Response:* *Section 6.2 (line 1735) states: "Was the study conducted primarily in a hypothesis generating or a hypothesis-testing mode?" Also, Table 2 (line 1764) takes into account whether a study has a pre-specified hypothesis; in this case such study will be rated as "high quality" regarding the study design and conduct.* *The following text has been added in line 1780. "Furthermore, results of exploratory research will need to be confirmed in future research before they can be used for risk assessment".*

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